2003. Applicants would especially like to thank the Examiners for taking the time to participate in the interview and contribute to the insightful discussion, which Applicants found to be extremely helpful.

Claims 25-27 have been canceled without prejudice in order to limit the issues and expedite prosecution of the remaining claims. Thus, rejections of Claims 25-27 are obviated and should be withdrawn. Claims 28-30 have been amended to clarify the antecedent basis for certain claim terms. Thus, the rejection of Claims 28-30 as indefinite under 35 U.S.C. §112, second paragraph should be withdrawn. Claims 5 and 6 have also been amended to delete dependencies from claims canceled upon entry of the instant amendment. New Claim 31 is fully supported by the specification of the present invention (*see, e.g.*, Figures 3 and 4), and thus does not constitute new matter.

After entry of this amendment, Claims 2-7, 10-15, and 28-31 will be pending in the application. For the Examiner's convenience, a copy of the pending claims is provided as Exhibit A.

1. **Interview Summary**

On May 14, 2003 an interview was conducted at the U.S. Patent and Trademark Office ("USPTO") during which the outstanding Office Action and the pending claims of the instant application were discussed. The applicants pointed out how the various claim terms, which carry their ordinary and customary meaning as understood by one skilled in the art, define the invention and distinguish it from the prior art. Applicants take this opportunity to establish for the record, the ordinary meaning of these claims terms, and to address the rejections of the claims.

2. **Claim Term Definitions**

The pending claims (*e.g.*, independent Claims 28-30 and claims dependent therefrom) are directed to a method for administration of a substance (*e.g.*, a drug), to a human subject comprising ***delivering*** the substance into the intradermal compartment of the human subject's skin.

The term "***delivering***" is used in the claims in accordance with its ordinary and customary meaning as understood by one skilled in the art – *i.e.*, the substance is targeted to or deposited in the intradermal space, and does not simply pass through it. As evidenced by its dictionary definition, the verb "deliver" or "delivering" means to "bring or transport to the proper place . . . ; distribute." (*See* Exhibit B, dictionary definition of the term "deliver" from *The American Heritage College Dictionary*, 2000, 3rd edition, Houghton Mifflin Company, Boston, New York (Reference CI)); "to send (something aimed or guided) to an intended target or destination" (*See* Exhibit B, dictionary definition of the term "deliver" from *Merriam-Webster's Collegiate Dictionary*, tenth edition, 1998, Merriam-Webster, Inc. Springfield, MA (Reference CJ)). Indeed, one skilled in the art of pharmacokinetics and drug delivery would understand that "***delivering*** the substance ***into*** the intradermal compartment" (*i.e.*, the words used in the claims) encompasses transporting, placing, or depositing the substance in the proper location, *i.e.*, the intradermal compartment. In the field of pharmacokinetics, ***delivering*** a drug encompasses the deposition of the drug to the target site where absorption and distribution of the drug occurs, *e.g.*, in this case absorption and distribution in the intradermal compartment (*E.g., see*, Exhibit C, *The Merck Manual of Diagnosis and Therapy*, 1999, Seventeenth edition, Beers and Berkow, *ed.*, Merck Research Laboratories, Division of Merck & Co., Inc. Whitehouse Station, N.J., pp. 2559-2567 at p.

2558, col. 2 entitled, "Parenteral Administration").[1] The instant specification uses the term consistently with its ordinary and customary meaning. For example, the specification explicitly states, "[t]o deliver a substance according to the invention, the needle is placed in the intradermal space and the substance is delivered through the lumen of the needle into the intradermal space where it can act locally or be absorbed by the blood stream and distributed systemically." (*see* the instant specification, p. 6, *ll.* 10-14)[2]. Thus, consistent with its customary usage, the claim term "delivering a substance into the intradermal compartment" means to transport or deposit a substance into that compartment, not just to simply pass that substance through the intradermal compartment.

Claims 29 and 30 are directed to a method for administration of a substance to a human subject comprising delivering the substance to the intradermal compartment so that *a pharmacokinetic profile similar to subcutaneous delivery* is achieved, but with either higher plasma levels or with a faster onset of detectable plasma levels. During the interview, the Examiner requested that Applicants address the meaning of this claim term to one skilled in the art. In this regard, we believe it beneficial to first review the basic principles of pharmacokinetics of drug delivery known to one skilled in the art as of the filing date of the instant invention.

An appropriate concentration of drug is required at the site of action to attain and maintain the pharmacologic response necessary for achieving therapeutic objectives. The pharmacologic response observed relative to the concentration of drug at the active site depends on the pharmacodynamics of the drug (*i.e.*, how the drug acts on the body); whereas, attaining and maintaining the appropriate concentration depends upon the pharmacokinetics of the drug (*i.e.*, how the body acts on a drug). Pharmacokinetics describes the concentration-time history of a drug in the body and is typically represented graphically by plotting the concentration of the drug in circulation over time.

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[1] We note that the phrase "intradermal delivery" of a drug (which is not the terminology used in the claims) has been used loosely in the art to refer to the administration of a drug to a subject via the subject's skin to unspecified depths, and does not require depositing the drug into the intradermal compartment where it is absorbed. (*e.g.*, *see* Gross at col. 3, *ll.* 39-42). This is also consistent with the dictionary definition of the noun "delivery" which means the act of throwing or discharging without any reference to intended targets or destinations. (*The American Heritage College Dictionary*, 2000, supra).

[2] Substances delivered in accordance with the methods of the invention are delivered to the blood or a fraction thereof, *e.g.*, serum, plasma, *etc.*

The pharmacokinetic profile of a drug may be simply assessed qualitatively, *e.g.*, by visual inspection of the graph, or by quantitating the following parameters: T_{max}, the time required for the drug to reach a maximum serum concentration; C_{max}, the maximum (or peak) serum concentration of the drug reached within a given dose and route of administration; T_{lag} (or "T_{onset}"), the delay time between the administration of a drug and the time for a measurable and detectable blood or plasma level of the drug; and the area under the serum concentration curve (AUC), which is a measure of bioavailability. (Exhibit C, The Merck Manual of Diagnosis and Therapy, 1999, Seventeenth edition, Beers and Berkow, *ed.*, Merck Research Laboratories, Division of Merck & Co., Inc. Whitehouse Station, N.J. (pages 2559-2562)

Pharmacokinetics is traditionally a comparative study, whereby the pharmacokinetic profiles of a drug given at different doses or routes of administration may be compared by visual inspection of the graphical representation. *See*, Exhibit C, *The Merck Manual of Diagnosis and Therapy*, 1999, at p. 2560, col. 2, 1st paragraph ("Drug products may be considered bioequivalent in extent and rate of absorption if their plasma-level curves are essentially superimposable. Drug products that have *similar* AUCs but differently shaped plasma-level curves are equivalent in extent but differ in their absorption rate-time profiles" (emphasis supplied).

This similarity is illustrated by the data presented in the instant specification in which the *pharmacokinetic profiles* of drugs delivered to the intradermal compartment of a subject's skin via the claimed methods are compared and contrasted with those profiles observed for subcutaneous delivery. As demonstrated by the working examples, delivery of a drug into the intradermal compartment of a subject's skin results in a systemic distribution of the drug with a *pharmacokinetic profile qualitatively similar to that achieved by conventional subcutaneous administration, but with a higher bioavailability, quantitatively higher plasma levels, and/or a faster onset of detectable plasma levels* (*see* instant specification at Examples 1 and 2 and Figures 1-5).

For instance, in Example 2, insulin was administered to the intradermal compartment of a pig animal model (*see* the instant specification at page 7, line 25 to page 8, line 21). The results are shown in Figure 4, where plasma insulin levels, subsequent to intradermal (ID) administration are plotted over time to generate a serum concentration – time curve (*i.e.*, its pharmacokinetic profile), which is compared to the pharmacokinetic profile observed for subcutaneous (SC) administration of insulin (for the Examiner's convenience, Figure 4 from the instant application is reproduced below).

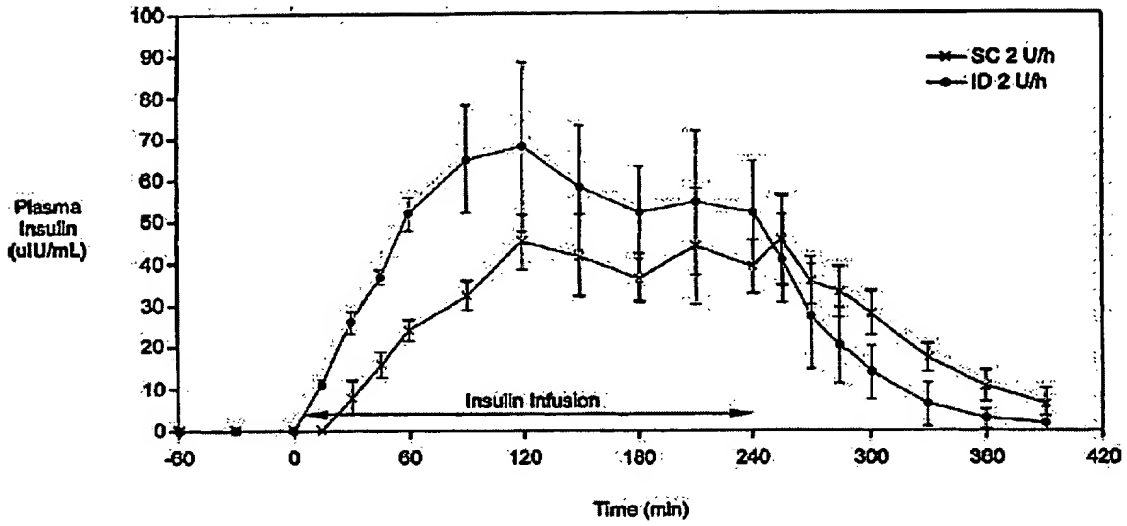

Figure 4. Pharmacokinetic profile of insulin as administered ID or SC. Plasma insulin levels are plotted as a function of time.

It is clear from a visual inspection of Figure 4 that the *pharmacokinetic profile* of insulin delivered to the ID space is *qualitatively similar* to that of SC, but differs quantitatively -- *e.g.*, achieving a higher plasma level (*e.g.*, delivering to the ID space results in approximately 10 to 30 units higher serum concentration of drug throughout the infusion as compared to SC administration), and a faster onset of detectable plasma level (*e.g.*, delivering to the ID space results in detectable plasma levels of drug as early as 15 minutes post injection, compared to more than 30 minutes observed for SC administration). Therefore, one skilled in the art would conclude, as the inventors report, that delivering insulin to the intradermal space results in a *pharmacokinetic profile qualitatively similar to that obtained by SC administration of insulin, but with a higher bioavailability, quantitatively higher plasma levels, and/or a faster onset of detectable plasma levels* (*see, e.g.*, the instant specification at p. 3, *ll.* 35-36; p. 6, *ll.* 2-4; p. 7, *ll.* 20-23; and Figures 3 and 4). This ordinary and customary interpretation is what is intended by the terminology used in the claims.

3. The Claimed Invention Is Not Anticipated by Gross

The rejection of the claims as anticipated by Gross (U.S. Patent No. 5,848,991) is in error and should be withdrawn.[3] Gross proposes methods and devices that non-selectively

[3] Claims 2-7, 10-15 and 25-27, are rejected as anticipated by Gross (Office Action, p.3). Although Claims 28-30 are not identified as rejected claims, Gross is discussed as

administer drugs below the epidermis. Gross does not describe delivering or targeting drugs into the intradermal compartment to achieve the systemic distribution and pharmacokinetic profiles claimed by Applicants. Thus, the claims are not anticipated by Gross, and the rejection should be withdrawn.

The claimed invention relates to delivering a substance, *e.g.*, a drug, into the intradermal compartment of a human subject's skin at a controlled volume and rate, so that the substance is systemically distributed in the plasma (Claim 28). By delivering a substance to the intradermal space in accordance with the instant invention a desired pharmacokinetic profile may be achieved, for example, a pharmacokinetic profile similar to subcutaneous delivery of the substance, but with higher bioavailability, quantitatively higher plasma levels and/or a faster onset of detectable plasma levels (Claims 29-30).

Contrary to the Examiner's contention, Gross does not describe, measure or evaluate the systemic distribution or pharmacokinetic profile of any drug, and therefore, does not expressly anticipate the claims.[4] Moreover, inherent anticipation cannot be found because the devices and methods described in Gross do not achieve the claimed systemic distribution and pharmacokinetic profiles of a drug targeted to the intradermal space. In fact, the data reported by Gross demonstrate that targeted delivery to the intradermal compartment is <u>not</u> achieved using the Gross devices.

For example, if Gross had actually delivered drug to the intradermal compartment, the entire dose of insulin administered in Example 1, *i.e.*, 20 I.U. of insulin, would have been distributed systemically in the animal's bloodstream.[5] As a result, the 20 I.U. of insulin would

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anticipatory to these claims (Office Action, p.3 last paragraph bridging over to p. 4). We are addressing the Examiner's comments regarding Gross with respect to Claims 28-30.

[4] (*See* Gross at col. 100, *ll.* 31-45) The Examiner erroneously contends that Gross describes the systemic distribution of drugs such as insulin and PTH, and describes pharmacokinetic profiles similar to subcutaneous delivery but with higher plasma levels (Office Action pp. 3-4). The Examiner's assessment of Gross is incorrect. Gross does not measure or report plasma concentrations of <u>drug</u> -- but instead uses an <u>indirect</u> pharmacodynamic measurement of serum glucose or calcium -- parameters that vary based on the physiological condition of the animal, independent of the drug. Similarly, the Applicants can find no mention of PTH in Gross. It would appear that the Examiner mistakenly attributed the Applicant's teachings regarding insulin, PTH and pharmacokinetics to Gross.

[5] According to Example 1, an insulin solution of 100 I.U./mL was infused to the rabbit at a rate of 0.1 mL/hour for two hours. Therefore, a total volume of 0.2 mL was administered (0.1 mL/hr. x 2hr. = 0.2 mL). 0.2 mL of an insulin solution of 100 I.U./mL translates into a total administration of 20 I.U. of insulin (0.2 mL x 100 I.U./mL = 20 I.U.)

have been bioavailable, and the animals treated in Example 1 would have died due to hypoglycemic shock.[6] *See*, Exhibit D, Marian *et al.*, 2001, *Acta Biologica Hungarica* 52(1): 35-45 and Sveinsson, 1939, *Investigations on the Influence of Insulin and Adrenalin in Rabbits with Alimentary Fatty Liver: The Effect of Insulin and Adrenalin on the Content of Fat and Glycogen in Liver and Muscles and on the Content of Fat and Sugar in Blood* (pp. 66-86), Oslo, Norway. Instead, the animals lived long enough for Gross to monitor blood glucose levels, which increased at the end of infusion (Gross, Fig. 12).[7]

A number of factors may explain the failure of Gross to deliver the full dose of insulin systemically -- but the "take-home" lesson is that targeted delivery to the intradermal space was not achieved! For example, the drug may have leaked out to the surface of the skin due to defective sealing; alternatively, inappropriate outlet depths may have resulted in subcutaneous or intramuscular delivery and lower bioavailability of drug. In other words, the parameters of needle lengths provided by Gross result in administration of the drug either at a depth too shallow to overcome the pressure exerted by the skin to achieve intradermal delivery of clinically useful amounts of the drug, or at a depth too deep so that subcutaneous drug delivery is achieved, rather than intradermal delivery.

In view of the foregoing, Gross does *not* teach *delivering* drug into the *intradermal compartment* of a subject's skin to achieve pharmacokinetic profiles as claimed in the instant application, and as such Gross does not anticipate the claimed invention. Anticipation can only be established by a single prior art reference that describes *each and every element* of the claimed invention. *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576, 18 U.S.P.Q. 2d 1896 (Fed. Cir. 1991). Nothing in Gross describes or even suggests *delivering* a substance into the intradermal compartment of a subject's skin for systemic distribution of the substance having the pharmacokinetic profiles claimed.

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[6] Had the entire bioavailable dose been delivered by any means described in the Gross patent, in the absence of intervention, the animals would have died due to hypoglycemic shock. Traditionally, 15-20 I.U. insulin has been used to induce hypoglycemia in experimental rabbits; without anesthesia or simultaneous administration of carbohydrates, the animals would fall into hypoglycemic coma and perish in the attendant convulsion. *See, e.g.*, Exhibit D, Sveinsson, 1939, *Investigations on the Influence of Insulin and Adrenalin in Rabbits with Alimentary Fatty Liver: The Effect of Insulin and Adrenalin on the Content of Fat and Glycogen in Liver and Muscles and on the Content of Fat and Sugar in Blood* (pp. 66-86), Oslo, Norway; Marian *et al.*, 2001, *Acta Biologica Hungarica* 52(1): 35-45).

[7] Again, we emphasize that Gross did not measure the pharmacokinetic profile or report any insulin levels in the animal's bloodstream -- instead, an *indirect* pharmacodynamic measurement of blood glucose was reported.

Moreover, Gross does not inherently anticipate the claimed invention. In order for a prior art reference to amount to an inherent anticipation of a claim, all the elements of the claim must *necessarily*, *inevitably* and *always* result from the prior art disclosure; mere possibilities or probabilities are not sufficient. *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981) (citing *Hansgirg v. Kemmer*, 102 F.2d 212, 214, 40 U.S.P.Q. 665, 667 (C.C.P.A. 1939). Furthermore, an accidental or unwitting duplication of an invention may not constitute an anticipation. *In re Marshall*, 198 U.S.P.Q. 344, 346 (C.C.P.A. 1978). Thus, in order for Gross to inherently anticipate the claimed invention, the method described in Gross must result in the claimed invention, *i.e. delivering drug into the intradermal space, thus achieving the claimed pharmacokinetic profile, each time and every time* Gross' method is practiced. *Glaxo Inc. v. Novopharm Ltd.* 53 F.3d 1043 (Fed. Cir. 1995). That is, each and every time Gross is practiced, its method must deliver the drug into the intradermal compartment so that systemic distribution having the claimed pharmacokinetics is achieved. However, as evidenced by the Gross patent itself in Example 1, the method disclosed in Gross *fails* to achieve delivery to the intradermal compartment, and therefore cannot anticipate the claimed invention.

Nothing in the remaining disclosure of Gross supplies the claimed features. Indeed, even Gross recognizes that its "intradermal device" does not specifically target the intradermal space, but rather haphazardly or non-selectively administers the drug "below the epidermis, *i.e.*, to the interface between the epidermis and the dermis or to the interior of the dermis or subcutaneously (*see* Gross at col. 3, *ll.* 39-42).[8] Consistently Gross characterizes the needles used in these devices as being of just sufficient length to penetrate through the epidermis." (Gross at col. 7, *ll.* 43-45, emphasis added.)[9] Even if Gross had used needles of the right length and configuration it would still not achieve intradermal delivery, as it also fails to appreciate the need for providing adequate pressures so that the substance is

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[8] Although Gross lists intradermal delivery as an *intended* feature of the purported invention, that is a far cry from having actually delivered or targeted drug into the intradermal space. As clearly illustrated by Gross' working Example, the proposed methods and devices do not achieve intradermal targeting.

[9] The Examiner erroneously contends that Gross provides an outlet at a depth of 500 μm to 2 mm in the skin, and the needle is about 300 μm to 2 mm long (Office Action at page 3, citing Gross, Figures 1-13; col. 4, *ll.* 10-35; col. 7, *ll.* 37-57). However, there is no teaching in Gross of needle outlet depths. It appears that the Examiner has improperly attributed disparate teachings from the Applicants' specification into the prior art. If, indeed, Gross contained this disclosure, it would be wrong and nonsensical –it is physically impossible to have an outlet depth that exceeds the length of the needle!

efficiently and consistently delivered to the intradermal compartment. In fact, Gross merely recognizes the need for sufficient pressure in order to pierce the stratum corneum, *i.e.*, "to stretch and pierce the epidermis" (*See* Gross at col. 3, *ll.* 25-31), but is silent on the need the for sufficient pressure to effectively discharge a substance so that effective delivery to the intradermal compartment occurs.

The instant specification, in contrast to Gross, provides the appropriate parameters to not only achieve targeted drug delivery to the intradermal space, but to do so in a controlled way (*e.g.*, controlled volume and rate) that will achieve a clinically useful distribution of the drug to the plasma.[10] It is the Applicants' disclosure, not Gross, which teaches the importance of not only the length of the needle, but the relative exposed height of the needle outlet (*e.g.*, the bevel) that could be used to successfully target the intradermal compartment. (*See*, specification at p. 4, *l.* 29 to p. 5, *l.* 21).

Thus, in view of the foregoing, Gross does not anticipate the claimed invention as it does not describe or even suggest delivering a substance to the intradermal compartment of a human subject's skin at a controlled volume and rate, to achieve a clinically useful systemic distribution of that substance with a pharmacokinetic profile similar to subcutaneous delivery, but with a higher plasma level, a faster onset of detectable plasma level, or a higher bioavailability. The rejections under 35 U.S.C. § 102(b) are in error and should be withdrawn.

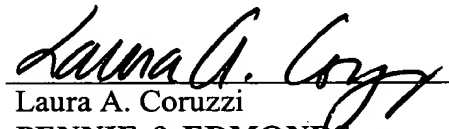
[10] The Applicants teach administration at a depth of 0.5 mm to 3 mm, preferably about 1 mm to 2 mm into the skin (*See* specification at p. 4, *ll.* 5-7), to achieve intradermal delivery. This can be accomplished using needles 2 mm long (preferably about 0.5 mm to 1 mm long), having outlet depths ranging from 0.25 mm to 2 mm (most preferably 1 mm) when the needle is inserted in the skin (*See* specification at p. 5, *ll.* 9-11).

CONCLUSION

In light of the above amendments and remarks, the Applicant respectfully requests that the Examiner enter the amendments and consider the remarks made herein. Withdrawal of all rejections, and an early allowance is earnestly sought. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

Respectfully submitted,

Date: July 10, 2003



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